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09/810,700	03/16/2001	Michael K. Wong	00-149-US	7224

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EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/810,700	WONG ET AL
	Examiner Karen A Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,3-8,10-20,23 and 24 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1,3-8,10-20,23 and 24 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1, 3, 4-8 and 14 have been amended. Claims 9, 21 and 22 have been canceled. Claims 23 and 24 have been added. Claims 1, 3-8, 10-20, 23 and 24 are pending and under consideration.
2. The text of sections of title 35 U.S code not found in this action can be found in a previous action.
3. The rejection of claims 1, 3-8 and 10-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. Newly added claims 23 and 24 are also rejected for failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to a genus of peptides which minimally comprise a charge motif of positive, positive, neutral-hydrophobic

Claim 1 is drawn to a purified peptide fragment with selective binding to tumor derived endothelial cells, wherein the peptide fragment possesses a charge motif of positive-positive-neutral hydrophobic, wherein the peptide fragment is not greater than fifty amino acid residues in length. Claim 3 embodies the purified peptide fragment of claim 1 wherein said peptide is operatively linked to a therapeutic agent capable of exerting a cytotoxic effect on a tumor. Claim 4 embodies the purified peptide fragment of claim 1 formulated as a pharmaceutical composition. Claim 5 embodies the purified peptide fragment of claim 1 wherein the peptide attached to a therapeutic agent is capable of exerting a cytotoxic effect on tumor vasculature sufficient to lead to tumor necrosis. Claim 6 embodies the purified peptide of claim 1 wherein said peptide fragment is linked to a diagnostic agent that is detectable upon imaging.

The claims are drawn to a genus of peptides which minimally comprise a three contiguous amino acid residues, where said three amino acids are positive, positive, neutral hydrophobic. The claim requires that said peptides have the functional attribute of selective-binding to tumor derived endothelial cells. The genus of claimed proteins is highly variant

because numerous structural alterations are tolerated in members of the genus which has the structural limitation of comprising only three required amino acids. Numerous functional attributes are also tolerated in members of the genus because the limitation "binding to tumor derived endothelial cells" reads on binding to any subcomponent of tumor derived endothelial cells, such as those taught by Epstein et al (WO 90/03801) to be fibronectin, laminin and type IV collagen (page 14, lines 18-24), as well as binding to any antigen which is selectively expressed in the vicinity of a tumor such as cell adhesion molecules responsible for adherence of PMN leukocytes, fibrin, fibrin degradation products and fibronectin (page 14, line 32 to page 15, line 3), the receptors flk and kdr, and heparin-containing proteoglycans as taught by Senger et al (US 6,022,541, column 6, lines 48-52), as well as the TIE2/Tek as taught by the abstract of Peters et al (British Journal of Cancer, 1998, Vol. 77, pp. 51-56). the instant specification describes SEQ ID NO:1-5 as having the claimed sequence motif and property of binding to tumor-derived endothelium. These sequences do not adequately describe the claimed genus, because the genus includes peptides which bind to numerous sub-endothelial components and antigens which are selectively accessible on, or selectively expressed by tumor associated endothelium. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus.

(B) As drawn to new matter

Claim 23 embodies the peptide of claim 1 wherein said peptide includes a cysteine residue at both the carboxyl and amino termini. Claim 24 embodies the peptide of claim 1 wherein said peptide includes a palindromic sequence on both the amino side and the carboxyl side of said charge motif. While it is noted that the originally disclosed peptides comprise a palindromic sequence of (CGG---GGC) and (CLL----LLC) this does not provide the basis for a broadly claimed "palindromic" motif which would include any amino acid sequence up to that which would be excluded by the provision of claim 1 specifying that the peptide is not greater than fifty amino acids in length. Further, claim 23 reads on a sequence of up to 50 amino acids residues having a cysteine at both the carboxyl and amino termini. Although the originally filed claims included claim 2 which embodies the peptide of claim 1 wherein the peptide was not greater than fifty amino acids in length, this does not support an dependent claim specifying that the sequence end in cysteine residues at both the carboxyl and amino termini. It is noted that the disclosed sequences having a cysteine at both the carboxyl and amino termini are 9 to 10 amino

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acids in length. Further, the disclosed sequences incorporate only two examples of palindromic sequences "GG" or "LL". This does not provide support for the broadly claimed palindromic motif.

The genus claimed by applicant would be reflected in a purified peptide with selective binding to tumor-derived endothelial cells, wherein said peptide consists of CysX₁X₂(positive amino acid)(positive amino acid)(neutral-hydrophobic amino acid)X₃X₄X₅Cys, and X₁=X₂=X₄=X₅; X₃= no amino acid or Arg; and wherein X₁=Gly or Leu.

Applicant argues that the limitation of selective binding to tumor cells would exclude that alternative presented by the examiner in the above rejection. This has been considered but not found persuasive. Selected binding to tumor cells is not interpreted as exclusive binding to tumor cells. If the tumor cell overexpresses constituents which are present on normal cells, an agent which binds to said constituent would be "selective" for the tumor cells because said agent would bind to tumor cells to a greater extent than normal cells by virtue of the upregulation of the target protein. Applicant argues that the instant specification teaches a manner in which a particular peptide may be tested to determine specific binding to tumor-derived endothelial cells. This has been considered but not found persuasive. The rejection for lack of an adequate written description is totally separate from that of lack of enablement. Because the specification provides an assay fro how to screen for the appropriate activity of the genus of peptides claimed does not necessarily provide a nexus to an adequate written description of the claimed peptides. Applicant argues that the flk and kdr receptors and TIE/Tek do not satisfy the claimed limitation of being less than 50 amino acids. This is not persuasive. The examiner was presenting flk and kdr receptors and TIE/Tek as targets for the claimed peptides which would result in the claimed peptides exhibiting tumor specificity. The examiner was not proposing that flk and kdr receptors and TIE/Tek were the claimed peptides, therefore the limitation of less than 50 amino acids has no bearing in the arguments against targeting the flk and kdr receptors and TIE/Tek.

Applicant argues that the assertion on page 4 of the previous Office action is unclear because all of the examples cited by the examiner are inapplicable to the claimed invention. This has been considered but not found persuasive. The claimed invention is a genus of peptides minimally comprising a charge motif and exhibiting selective binding to tumor endothelium. As

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such the binding of the claimed peptides to flk and kdr receptors and TIE/Tek are within the scope of the claims.

4. The rejection of claims 1 and 3-5 under 35 U.S.C. 102(a) as being anticipated by Smith et al (WO 00/04052) is maintained for reasons of record.

Smith et al disclose a pharmaceutical composition for treating a established primary tumor and for preventing the growth of secondary tumors following surgery (page 15, lines 24-26). Smith et al disclose that said composition comprise structure which comprise anti-angiogenic agents linked to a peptidic membrane binding entity (page 4, lines 2-10). Smith et al teach a specific peptidic membrane binding entities which are SEQ ID NO:12 (page 4, line 26 to page 5, line 3). SEQ ID NO:12 contains "Lsy-Arg-Phe", and SEQ ID NO:13 and 14 contain "Lys-Lys-Ser" which fulfill the limitation of claim 1 with respect to the claimed binding motif of positive-positive-neutral hydrophobic. Smith et al disclose that the membrane binding element associated with the anti-angiogenic peptide has affinity for the vascular endothelium of growing vessels (page 2, lines 20-24, and abstract, lines 1-3). Smith et al disclose that the membrane binding elements have low affinities for membrane components but high affinities for blood vessel endothelium (page 2 line 30 to page 3, line 2). Smith et al do not specifically state that the anti-angiogenic agent attached to the membrane binding element is capable of inducing tumor necrosis. However, an anti-angiogenic agent inhibits the formation of new blood vessels at the tumor site, thus depriving the growing tumor of oxygen and nutrients. Smith et al discloses the administration of the angiogenesis -inhibiting agent comprising the peptidic binding elements for treating a established primary tumor. It would be inherent in this treatment that the growing tumor would undergo necrosis because it would be deprived of an increasing supply of oxygen and nutrients.

Applicant argues that because Smith et al do not disclose SEQ ID NO:12, 13 and 14 to specifically bind to tumor derived endothelial cells they do not anticipate the instant claims. This has been considered but not found persuasive. SEQ ID NO:12, 13 and 14 contain the minimal charge motif required by claim 1. Smith et al disclose that the SEQ ID NO:12, 13 and 14 are membrane binding elements which have affinity for vascular endothelium of growing vessels. As stated above, the recitation of specific binding to tumor derived endothelial cells does not

exclude binding to growing blood vessels. Further, it is recognized in the art that the formation of new blood vessels, and thus the growing of new endothelium takes place around a tumor in order to assure an adequate amount of nutrients and oxygen for said tumor. Thus an agent which binds to growing endothelium of blood vessels would be expected to bind to tumor-derived endothelium. Applicant has not provided any data to demonstrate that SEQ ID NO:12, 13 and 14 would not bind to tumor derived endothelium or that the instant disclosed peptides would not bind to new blood vessels.

5. The rejection of claims 1 and 3-6 under 35 U.S.C. 103(a) as being unpatentable over Smith et al (WO 00/04052) in view of Epstein (WO 90/03801) is maintained for reasons of record.

Smith et al teach the peptides of SEQ ID NO:12-14 which are linked to anti-angiogenic agents for the treatment of primary tumors or metastatic tumors after removal of said primary tumor. Smith et al do not teach a diagnostic agent that is detectable upon imaging linked to SEQ ID NO:12-14.

Epstein et al teach a delivery vehicle having the ability to concentrate at the site of neoplastic tissue wherein said delivery vehicle is conjugated to a tumor imaging agent (page 9, lines 32-35). Epstein et al teach delivery vehicles having specificity for sub-endothelial components of the blood vessel wall that become accessible in structurally abnormal endothelium associated with tumors (page 14, lines 18-24) Epstein et al also teach delivery vehicles that bind to antigens selectively expressed upon tumor associated endothelial cells (page 14, line 34 to page 15, line 3).

It would have been prima facie obvious at the time the invention was made to link the peptidic membrane binding elements as taught by Smith et al to have high affinity for tumor endothelium to a tumor imaging agent as taught by Epstein et al. One of skill in the art would have been motivated to do so by the teachings of Epstein et al on the concentration of tumor imaging agents at the site of the neoplastic tissue by agents having affinity for vascular endothelium associated with tumors.

Applicant argues that because the delivery vehicle of Epstein are based upon metabolic effects and by allowing antibodies to accumulate at the tumor they somehow teach against the

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specific binding to tumor endothelial cells. Applicant also argues that the immuno-proteins of Epstein are longer than 50 amino acids. Applicant concludes that there would be no reason at all that one of skill in the art would combine the teachings of Epstein with peptides of 50 amino acids or less. This has been considered but not found persuasive. Epstein et al is not relied upon for the identity of the peptides which bind to tumor derived endothelial cells but for the identity of a diagnostic agent that is detectable upon imaging. One of skill in the art would recognize that the membrane binding element associated with growing blood vessels would concentrate in the vicinity of the tumor endothelium because a tumor causes new blood vessels to form to insure adequate supply of oxygen and nutrients which parallels the continues tumor growth. Epstein teaches delivery vehicles that bind to antigens selectively expressed by tumor associated endothelial cells (page 14, line 34 to page 15, line 3). One of skill in the art would recognize that the binding to antigen selectively expressed by tumor associated endothelial cells would encompass the membrane binding elements associated with growing blood vessels such as SEQ ID NO:12, 13 and 14 as taught by Smith et al. Thus, there would be ample motivation to combine the teachings of Smith et al and Epstein et al.

6. The rejection of claims 1 and 4 under 35 U.S.C. 102(a) as being anticipated by Oku et al (WO 00/23476) is maintained for reasons of record.

Oku et al disclose SEQ ID NO:3 which has the claimed sequence motif of "Arg-His-Val" in a 15-mer amino acid sequence (page 2 of the sequence listing). The abstract of Oku et al teach that SEQ ID NO:3 is a neovascular-specific peptide. The abstract teaches that the disclosed peptide is useful for the treatment and diagnosis of cancer. Because the peptide is a neovascular-specific peptide it will bind to tumor endothelium that is developing as a result of angiogenesis and fulfill the specific embodiment of claim 1 with regard to selective binding to tumor derived endothelial cells.

7. The rejection of claims 1 and 3-6 under 35 U.S.C. 103(a) as being unpatentable over Epstein (WO 90/03801) in view of Oku et al (WO 00/23476) is maintained for reasons of record.

Epstein et al teach conjugates of delivery vehicles having the ability to locate at neoplastic sites (page 13, lines 20-23). Epstein et al teach delivery vehicles that have specificity

for components of the endothelium that become accessible in tumor endothelium (page 14, lines 18-24) and delivery vehicles with specificity for antigens selectively expressed in vascular tissue in the vicinity of tumors (page 14 lines 32 to page 15, line 2). Epstein et al teach a delivery vehicle having the ability to concentrate at the site of neoplastic tissue wherein said delivery vehicle is conjugated to a tumor imaging agent (page 9, lines 32-35). Epstein et al do not teach a delivery vehicle having the claimed sequence motif which is not greater than fifty amino acid residues.

Oku et al teach SEQ ID NO:13 binds specifically to neovascular endothelium. (abstract). SEQ ID NO:3 has the claimed motif of "Arg-His-Val" in a 15-mer amino acid sequence (page 2 of the sequence listing). the abstract teaches that the disclosed peptide is useful for the treatment and diagnosis of cancer.

It would have been prima facie obvious at the time the claimed invention was made to substitute the peptide taught by Oku et al for a delivery vehicle taught by Epstein et al. One of skill in the art would have been motivated to do so by the teachings of Oku et al that SEQ ID NO: 3 binds to neovascular endothelium. Because the peptide is a neovascular-specific peptide it will bind to tumor endothelium that is developing as a result of angiogenesis and fulfill the specific embodiment of claim 1 with regard to selective binding to tumor derived endothelial cells., and thus fulfill the criteria of Epstein et al on a delivery vehicle to tumor derived endothelium.

Applicant argues that the peptides of Oku et l would bind to any neovasculature including that found in would healing, retinopathy and inflammation and thus do not meet the limitation of binding to tumor associated endothelial cells. This has been considered but not found persuasive. The recitation of tumor associated endothelial cells does not exclude the binding to new blood vessels because it would be expected that the new blood vessels associated with tumor cells would exhibit the same antigens as new blood vessels associated with wound healing, and inflammation. Applicant has not provided evidence that the peptide of Oku et al would not bind to tumor associated endothelium, or that the instant disclosed peptides would not bind to neovasculature formed from wound healing and inflammatory processes.

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8. It is noted that the binding of the claimed peptides to tumor derived endothelial cells was determined using the binding to NIH3T3 cells as a negative control. NIH3T3 cells are not normal endothelial cells, nor are they endothelial cells derived from neovasculature related to inflammation or wound healing. Further the peptides were injected into mice bearing tumors but were not contrasted to mice having neovasculature associated with wound healing or inflammation. Thus, applicant is arguing a degree of specificity which is not supported by the specification.

9. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments and arguments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

11/15/2004

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